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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/411,006	10/01/1999	ROSS WALDEN TYE	07207.0002US	7762

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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/411,006	TYE, ROSS WALDEN	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- Th MAILING DATE of this communication app ars on the cover she t with the correspond nce address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,27,29,35,42,44,49-51,53,56-58,60,63 and 64* is/are rejected.

7)☒ Claim(s) *20-26,28,30-34,36-41,43,45-48,52,54,55,59,61 and 62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 7 is acknowledged. Claims 1-64 have been examined in this application and the office action follows below.

2. Applicants' remarks regarding the previous office action have been considered. It should be noted that the reference of Marschall et al. (US 5380824) should have been applied rather than Bucci et al. and the entire pinpoint citations were with regards to Marschall. As such, the previous rejection has been withdrawn and a new grounds for rejection follows below. The rejection is entirely the same as the previous office action but the appropriate references have now been applied. In an attempt to facilitate furtherance of prosecution, any arguments raised by applicant with respect to Tye et al. and Rausch et al. are addressed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-19, 27, 29, 35, 42, 44, 49-51, 53, 56-58, 60, 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tye (4529719) in view of Marschall et al. (US 5380824) and Rauch et al. (5084558).

The claims are drawn to a non pyrogenic, endotoxin free, oxygen free, stroma free, cross-linked hemoglobin, cross linked with bis dibromo salicyl fumarate and modified by pyridoxal-5'-phosphate.

The reference of Tye et al. teach a stroma free tense state tetrameric hemoglobin cross linked with bis(3,5-dibromosalicyl)-fumarate and modified with pyridoxal-5'-phosphate (see claim 1 and 3 of the patent). The modified hemoglobin serves as a blood substitute product with a storage life of greater than two years (see col. 6, lines 50-64). Further, the modified hemoglobin has "superior oxygen transport capabilities not found in stroma free hemoglobin" (see col. 7, lines 5-11). The method of making the modified hemoglobin involves the isolation of hemoglobin, subjecting the solution to a vacuum and flushing with inert gas until the oxygen tension is decreased at a value of 1.0mm Hg, reacting with bis(3,5-dibromosalicyl)-fumarate (BDBF), finally modifying with pyridoxal-

5'-phosphate (see col. 9, lines 39-68 and col. 10, lines 1-36). The source of the hemoglobin can include human, bovine, bovine, or porcine (see col. 8, lines 17-20). The difference between the prior art and the instant application is that the reference does not teach removing endotoxin from preparation containing red blood cells, removing oxygen from red blood cells, and lysing red blood cells.

However, Marschall et al. states that it is necessary to have the hemoglobin in deoxy form for the pyridoxylation with pyridoxal-5'-phosphate (see col. 3, lines 58-62). The reference teaches various methods for deoxygenation hemoglobin prior to pyridoxylation. One method involves the suspension of red blood cells with a reducing agent to maintain the solution in deoxy form (see col. 4, lines 53-68). The solution with the red blood cells is then subjected to a heating step that lyses the cells and extracts the free reduced hemoglobin (see col. 5, lines 23-30). Before the polymerization, the solution is subject to precipitation and centrifugation to remove all of the organic and inorganic material from hemoglobin (see col. 5, lines 57-64). The reference further states that the reducing agent maintains the environment oxygen free. Moreover, although not necessary, an atmosphere of an inert, oxygen free gas may be present, such as nitrogen or argon. The reference states, however, the "necessary reaction condition in this respect maintaining an oxygen free atmosphere] can easily be determined by a person skilled in the art" (see col. 4, lines 53-68 and col. 5, lines 39-44). Note that Tye teach that the environment can be maintained oxygen free by purging the environment with an inert gas and removing the gas by vacuum (see Tye col. 10, lines 3-5). Finally, Bucci et al. teach that the starting material can also be blood cells which have been subject to lysis and from which the stroma has been removed completely or partially (see col. 3, lines 43-46).

Rausch et al. acknowledges that Tye et al. Does not teach that the hemoglobin preparation is endotoxin free (see col. 5, lines 60-66). The reference states that endotoxin causes fever, diarrhea, hemorrhagic shock, and other tissue damages (see col. 12, lines 32-37). Therefore, a low concentration of endotoxin is desired. Rauch also discloses that the hemoglobin can be crosslinked after removal of endotoxin and red-blood cell clarification (see col. 12, lines 67-68). The reference also teach that the product obtained has a phospholipid concentration of less than about 1 nanogram per mL (see claim 9). Further, during the ultrafiltration stage, a process used to remove endotoxin, pyrogen are also removed since pyrogen are between 100,000 and 1 million in molecular weight (see col. 17, lines 46-55). Thus, the reference discloses that when endotoxin free hemoglobin is obtained, the process yields a pyrogen free product as well. Therefore, in order to achieve a endotoxin concentration of .5EU/mL, it would have been obvious to optimize the initial cell separation, as disclosed by Rausch, to avoid complications such as caus fever, diarrhea, hemorrhagic shock, and other tissue damage that are associated with endotoxin. It would have been further obvious to one of ordinary skill in the art to utilize the method disclosed in Bucci et al. to maintain the hemoglobin in deoxygenated from because deoxy-hemoglobin is necessary for polymerization to occur.

Response to Arguments

In the response, Applicants argued that Ruasch et al. cannot be combined with Tye because Rausch believes the approach taken by Tye to be inadequate. Because the Background Section of Rauch et al. discusses the inadequacies of the state of the art, Applicants argue that Rauch considers the Tye patent to be inadequate.

However, the reference of Rauch was cited to provide motivation why one would want to remove endotoxins from hemoglobin preparation. Indeed the rejection acknowledges that Tye is

inadequate since the Tye is deficient in any teaching with regard to removal of endotoxins. Therefore, in order to achieve a endotoxin concentration of .5EU/mL, it would have been obvious to optimize the initial cell separation, as disclosed by Rausch, to avoid complications such as cause fever, diarrhea, hemorrhagic shock, and other tissue damage that are associated with endotoxin. Thus, it is wholly appropriate to combine Tye with Rauch.

Applicants also argue that there is no teaching of "removing oxygen from [a] preparation containing red blood cells." However and as stated above, Marschall teaches a method that involves the suspension of red blood cells with a reducing agent to maintain the solution in deoxy form. The solution with the red blood cells is then subjected to a heating step that lyses the cells and extracts the free reduced hemoglobin. Before the polymerization, the solution is subject to precipitation and centrifugation to remove all of the organic and inorganic material from hemoglobin. The reference further states that the reducing agent maintains the environment oxygen free. Thus, the reference also teaches that oxygen is removed from the lysed red blood cells.

4. Claims 20-26, 28, 30-34, 36-41, 43, 45-48, 52, 54-55, 59, 61-62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The claimed subject matter of claim 20 and the like, which claims the removal of oxygen by centrifuging the red blood cells under vacuum, and claim 22 and the like, which claims washing of surface which will come into contact with the cross-linked hemoglobin with a dilute solution of a hemoglobin, is neither taught nor suggested by the prior art of record.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

11/16/03
Anish Gupta